Ensuring a Robust NIH Clinical Trial Enterprise

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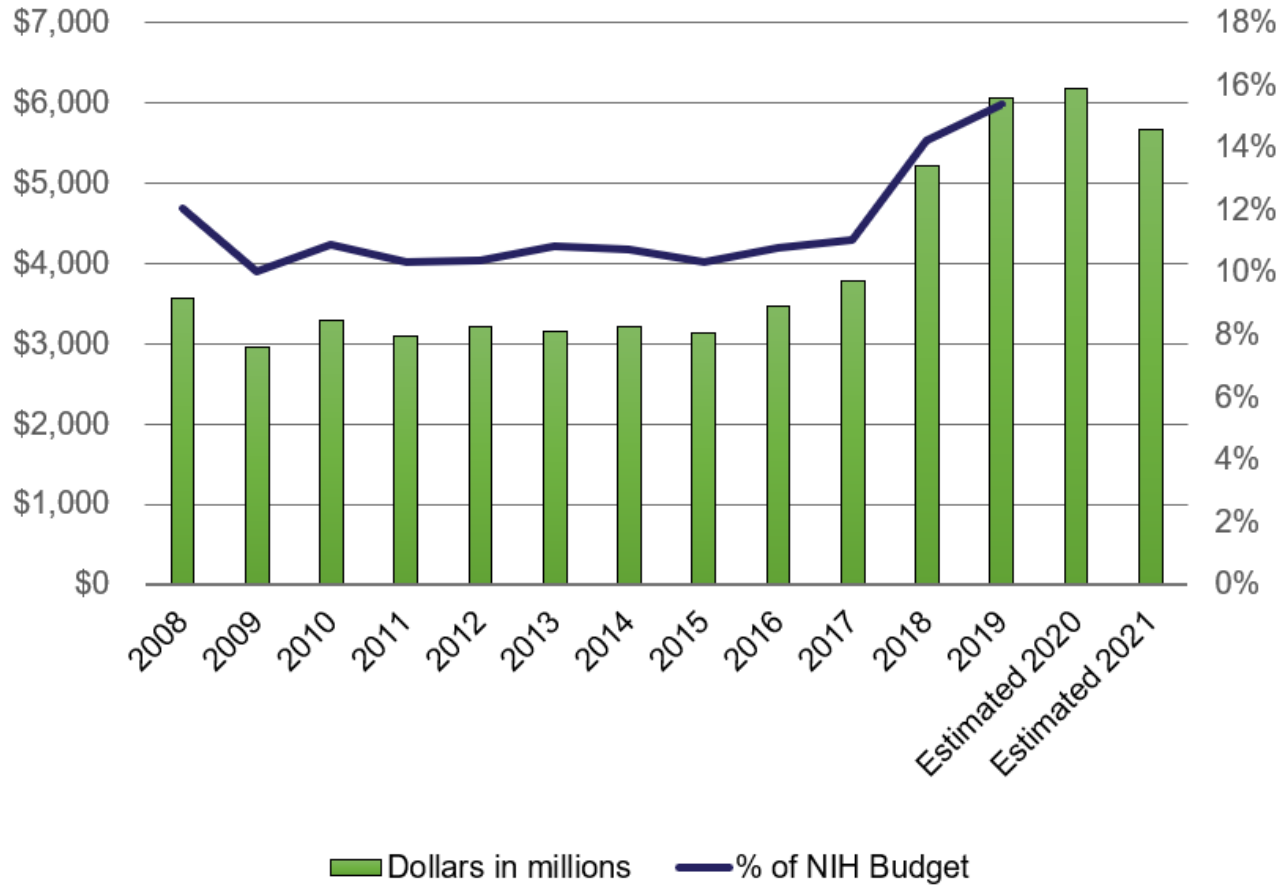
Vital Importance of Clinical Trial Stewardship

- NIH committed to responsible stewardship
  - $18B investment in clinical research; over $6B supports clinical trials
  - Ensuring appropriate management, oversight and efficiency of CT enterprise essential to NIH mission
- Generate best possible evidence to support public health, clinical care
- COVID-19 highlighted need for further efficiency and inclusiveness in CTs

NIH "Clinical Trials and Supportive Activities"



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Key Principles of CT Oversight and Conduct

- Protect and support participants
- Ensure that research is meaningful to participants and public
- Ensure effective research/trial design and management to maximize benefit to public and conserve NIH resources
- Promote transparency, trust and communication of all clinical research conduct and results

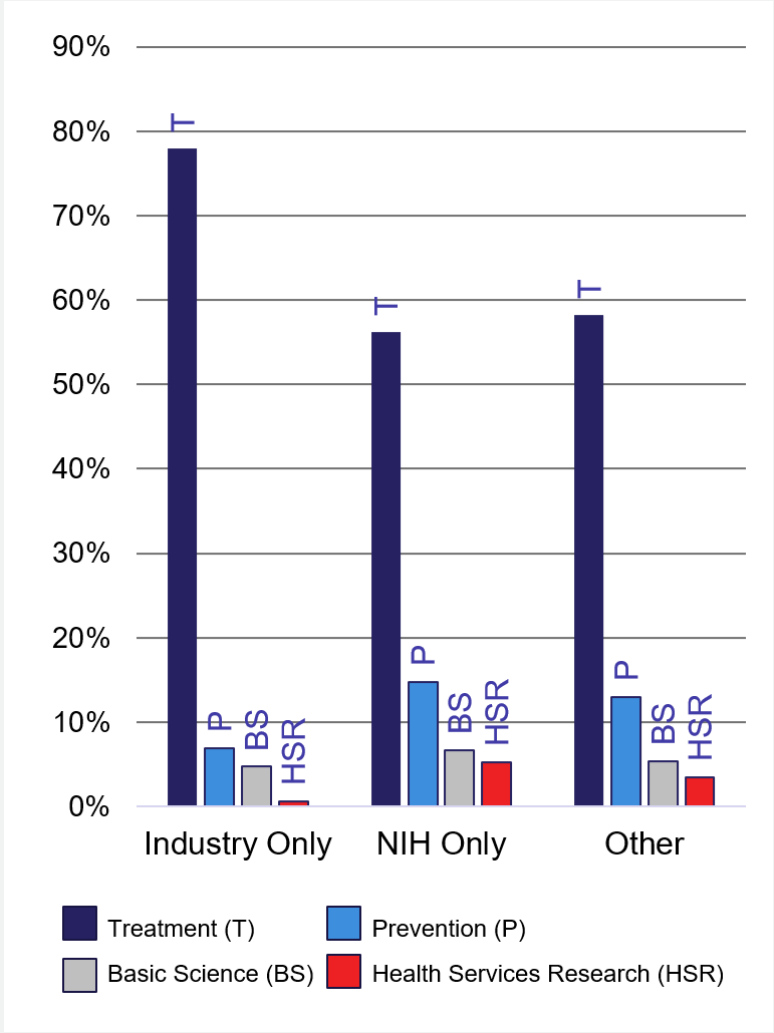
Characteristics of NIH-funded CTs; Trends over time in CT.gov registered studies, 2005 – 2023 (M. Lauer)

- 290,495 trials registered
  - NIH funded 7%
  - Industry funded 33%
  - Other (institutions, private foundations) funded 60%
- Most trials conducted by *all* sponsors are small and single-center
- Change in NIH portfolio over time: fewer treatment, drug trials; more prevention, behavioral trials
- Large number of grant mechanisms support clinical trials (R, U, P, K and others), networks
  - U grants (cooperative agreement) more likely to be classified as a 'Phase' (1 or 3) trial, to be multi-center and to focus on drugs/biologics
  - R01 mechanism more likely to fund basic science, prevention, health services research, and to test behavioral interventions
  - Some trials funded through established networks, contracts, OTAs

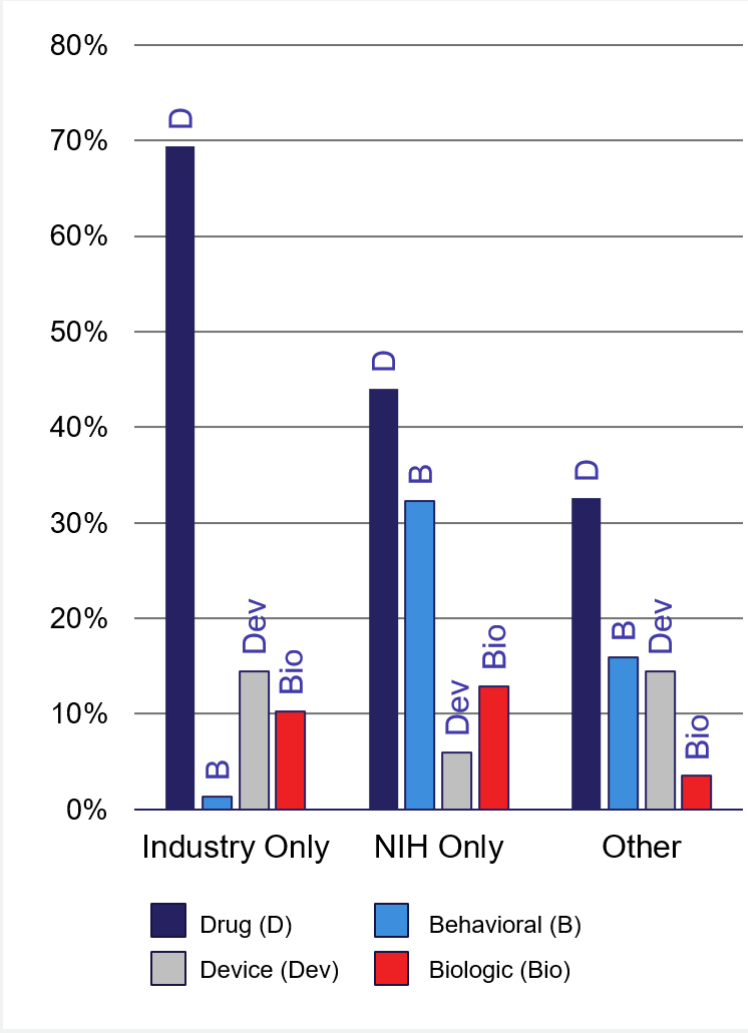
Trial Characteristics According to Sponsor

Source: Michael Lauer, MD (NIH OER)

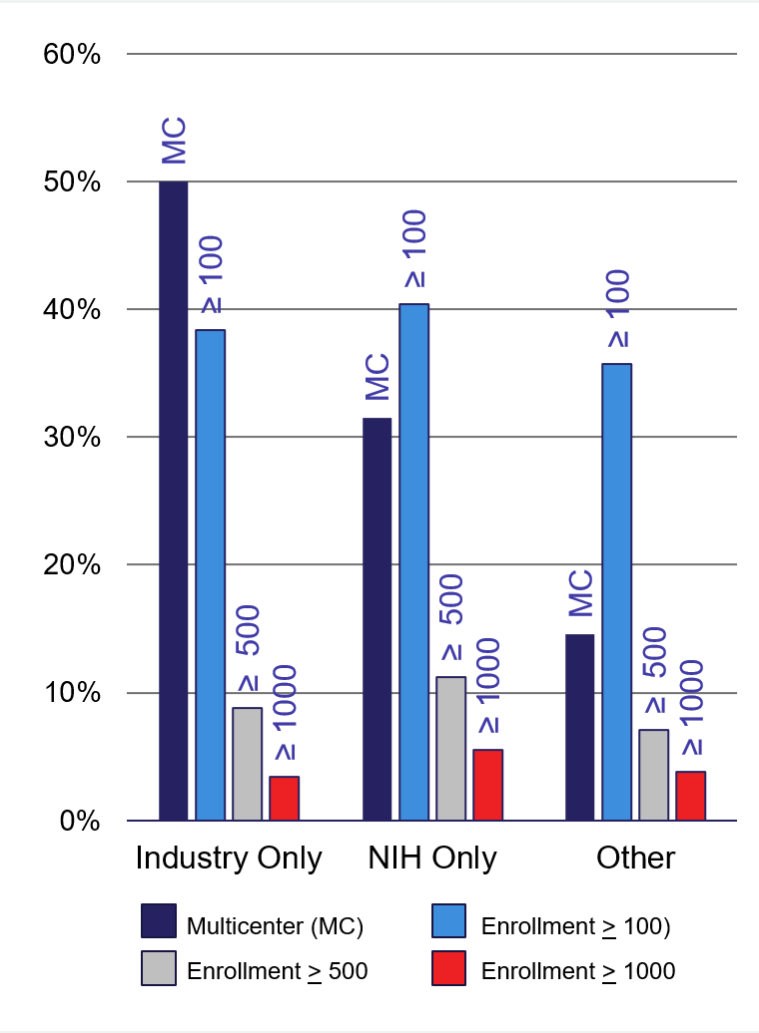
Primary Purpose



Type of Intervention



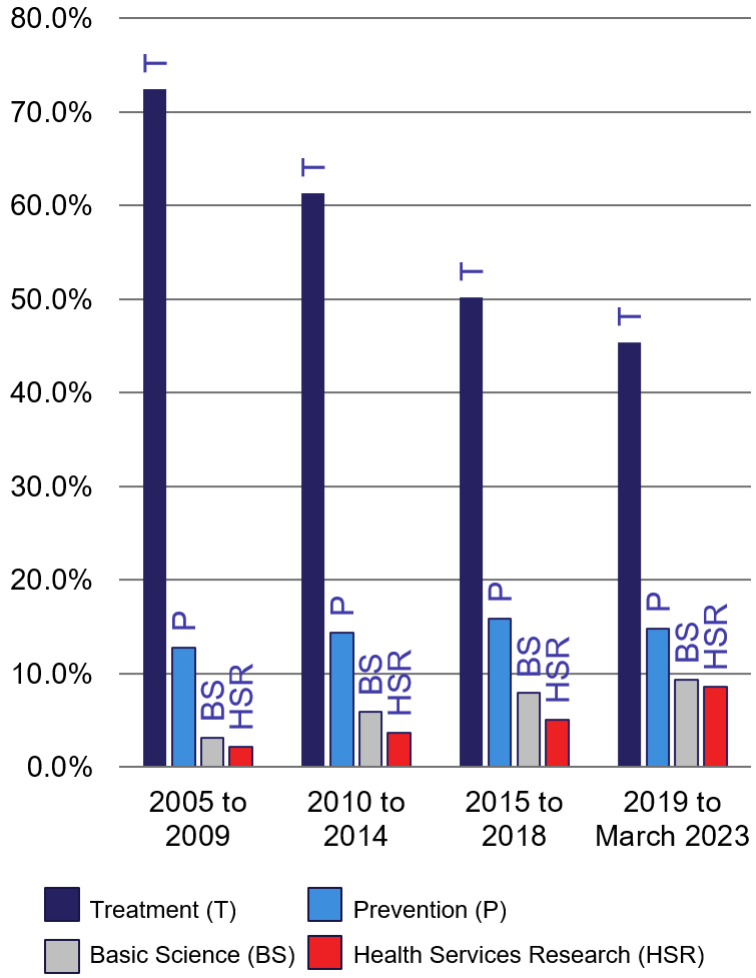
Enrollment



NIH Trial Characteristics According to Year of Registration

Source: Michael Lauer, MD (NIH OER)

Primary Purpose



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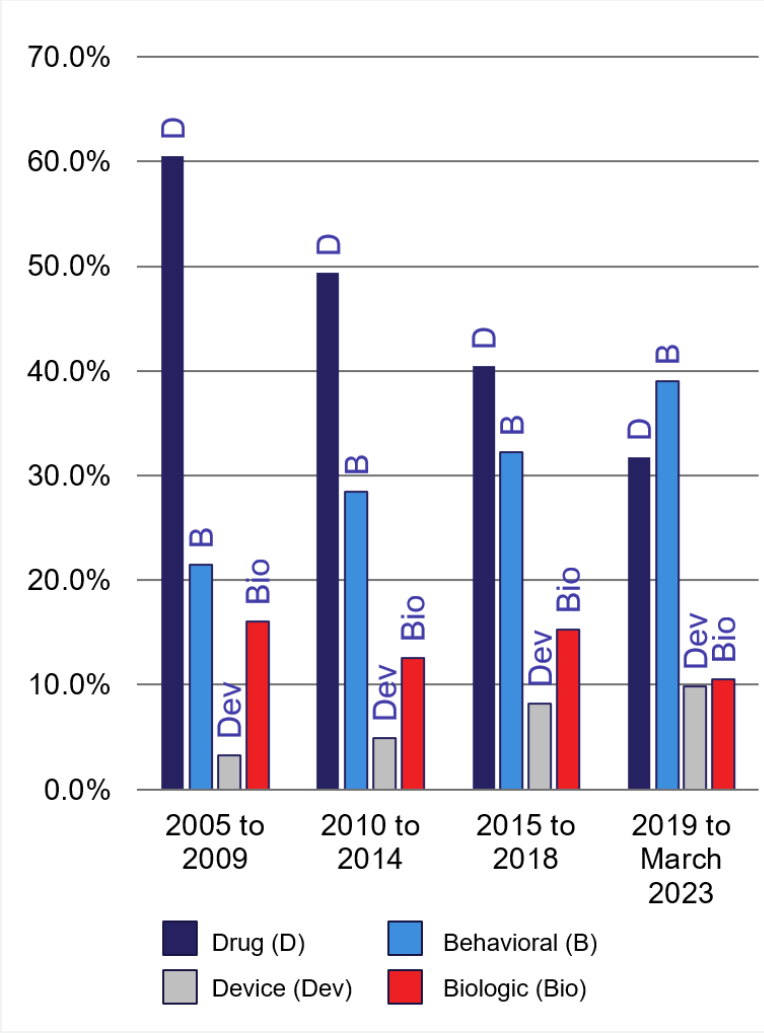

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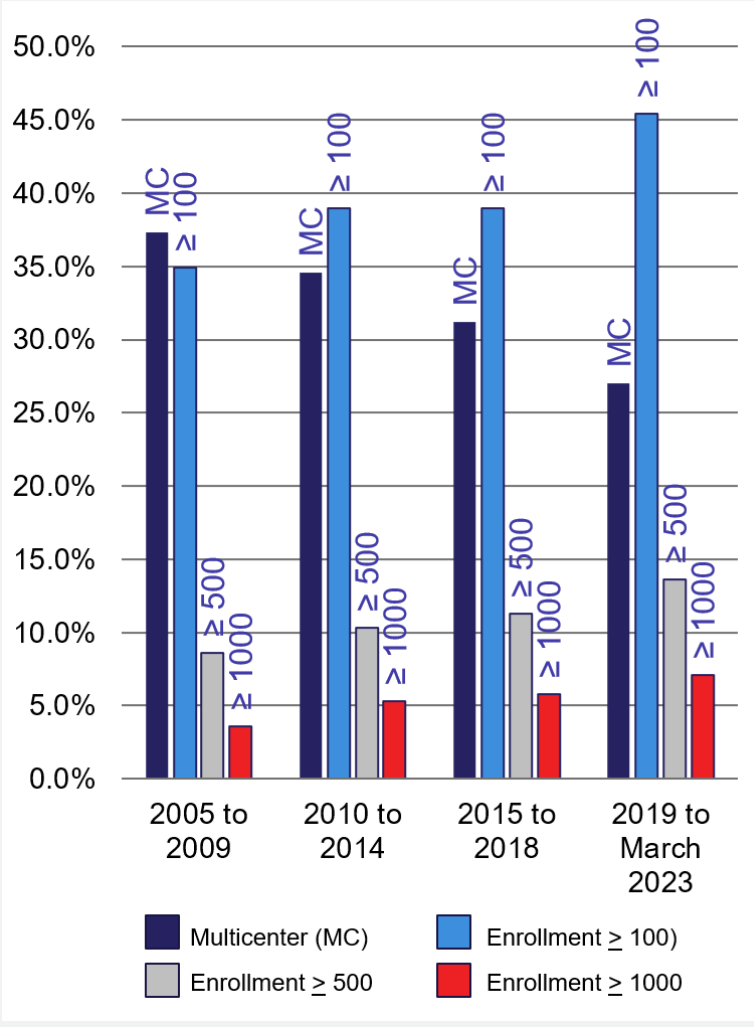


Clinical Trial Stewardship Task Force, 2021 - 2022

- Background
  - Periodic review of NIH clinical research/clinical trial processes to evaluate and adjust policies and procedures to optimally support our portfolio, for both extramural and intramural research
  - Last reviewed by 2014 Task Force; during 2016 – 2020, NIH developed resources, tools, dedicated funding announcements, and training for NIH staff, peer reviewers and investigators to support implementation
- New Task Force convened with wide representation across NIH;
  Charge: to evaluate -
  - Progress of prior policy reforms (5 year)
  - Efficiency, interoperability and oversight of current CT network operations and capabilities of operations to support public health needs
  - Implementation of NIH inclusion policies & opportunities to further enhance diversity and inclusion in clinical research

Task Force Membership

Lyric Jorgenson, OD (co-chair)
Michelle Culp, OD (staff lead)
Martha Barnes, NIEHS
Robin Boineau, NICCH
Noni Byrnes, CSR
Michael Chiang, NEI
Janie Clayton, OD
Lindsey Criswell, NIAMS
Jim Doroshow, NCI
Rena D'Souza, NIDCR
Greg Germino, NIDDK
Michael Gottesman, OD
Jonathan Green, OD
Michael Kurilla, NCATS
Cliff Lane, NIAID

Debara Tucci, NIDCD (co-chair)
Mike Lauer, OD
Janice Lee, NIDCR, OD
Raye Litten, NIAAA
Teri Manolio, NHGRI
Anna Ordóñez, NIMH
Amy Patterson, NHLBI
Sergei Romashkan, NIA
Carmen Rosa, NIDA
Caroline Signore, NICHD
Monica Webb Hooper, NIMHD
Becky Williams, NLM
Clinton Wright, NINDS
Shannon Zenk, NINR

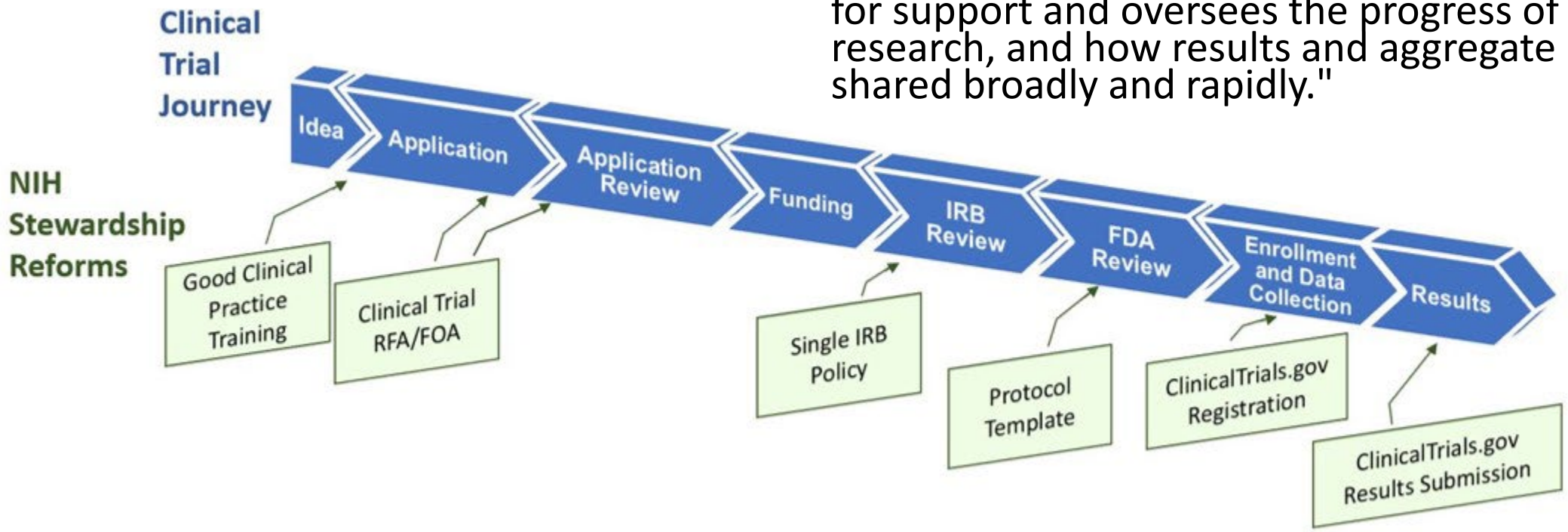
2016 Reforms Target the Clinical Trial Lifecycle

VIEWPOINT

Toward a New Era of Trust and Transparency in Clinical Trials

Hudson, Lauer, & Collins, JAMA 2016

"NIH has launched a multifaceted effort to improve the quality and efficiency of clinical trials … These initiatives will reengineer the process by which clinical investigators develop ideas for new trials, how NIH reviews and selects clinical trials for support and oversees the progress of the research, and how results and aggregate data are shared broadly and rapidly."



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https://nexus.od.nih.gov/all/2016/09/16/clinical-trials-stewardship-and-transparency/

Outline

- **Review six consolidated recommendations of the Task Force**
  - Challenges and needs identified
  - Specific recommendations
- **Summary of challenges across NIH**
- **Discussion of NIH vision and unique role in national clinical research and clinical trial ecosystem**

Develop strategies to coordinate and leverage NIH investment in clinical trial infrastructure

Challenges and Needs Identified

Define and track clinical trial investments and associated infrastructure

- Currently no NIH-wide definition of ‘clinical trial network’, and no unique identifiers of CTNs or associated CTs
- Once defined, identify CTNs NIH-wide, including purpose, structure, capabilities, funding mechanism, ‘best practices’
- Understanding characteristics/ capabilities could inform policies that lead to enhanced CT efficiency and adaptability (ongoing and during PHE)
- Knowledge of existing NIH networks, resources and infrastructure could facilitate partnerships among ICOs

Identify best funding mechanisms for support of clinical trials

- Funding mechanisms used: grants, contracts, Other Transaction Authorities (OTAs)
- Varies by IC based on experience and staff preference, but could possibly be leveraged more strategically

Identify and strategically engage with potential partners (per ACTIV)

- FDA, PCORI/PCORnet, Frederick National Laboratory, others

Maximize effectiveness and efficiency of clinical trial oversight, and facilitate and define trial 'success'

Challenges and Needs Identified

ICOs have very different resources and processes for monitoring clinical trials

NIH does not have standard metrics to monitor clinical trial conduct and progress

- Clinical Trial Operations Working Group (CTOW) recently spearheaded documentation of SOPs
- Need for established metrics to capture: enrollment targets and rates (including those related to race/ethnicity, sex/gender, and age); IRB approval, primary endpoint reached, and others determined to be of importance
- Ongoing and consistent monitoring facilitates progress and accountability

Are there metrics and milestones that help predict successful completion of a clinical trial?

- Success of a trial can be identified in a number of ways: meet enrollment target, meet enrollment target on time, prove/disprove hypothesis, publication, implementation in clinical practice to improve health
- Process to inform continuous review and 'stopping rules' for underperforming trials, to maximize responsible use of NIH and participant resources (time, money, trust)

NIH staff are often the experts in CT design and conduct, and support PIs who are the SMEs

- NIH staff burden is significant: create more efficient systems to support staff NIH-wide, decrease burden

NIH

Establish consistent, high quality clinical trial review processes across NIH

Challenges and Needs Identified

Extramural review of Clinical Trial–specific FOAs

- 2023 – NIH Steering Committee and leadership approved the integration of rigorous clinical trial evaluation into the simplified review framework for RPGs

Other clinical trials funding mechanisms

- Intramural research
- Contracts and OTAs
- Research conducted through established/funded networks

Need to ensure consistency of review across all mechanisms used at NIH

Acknowledgement that review is multi-layered

- both scientific and operational/feasibility review

Establish policies that elevate diversity, equity, and inclusion in the recruitment and retention of participants in clinical research

Challenges and Needs Identified

Improve monitoring of diverse participants in research

- Increase interoperability of NIH data systems to improve access and usability of inclusion-related data
- Enhance training for staff to improve quality of review of inclusion plans
- Consider actions to improve accountability for meeting enrollment goals

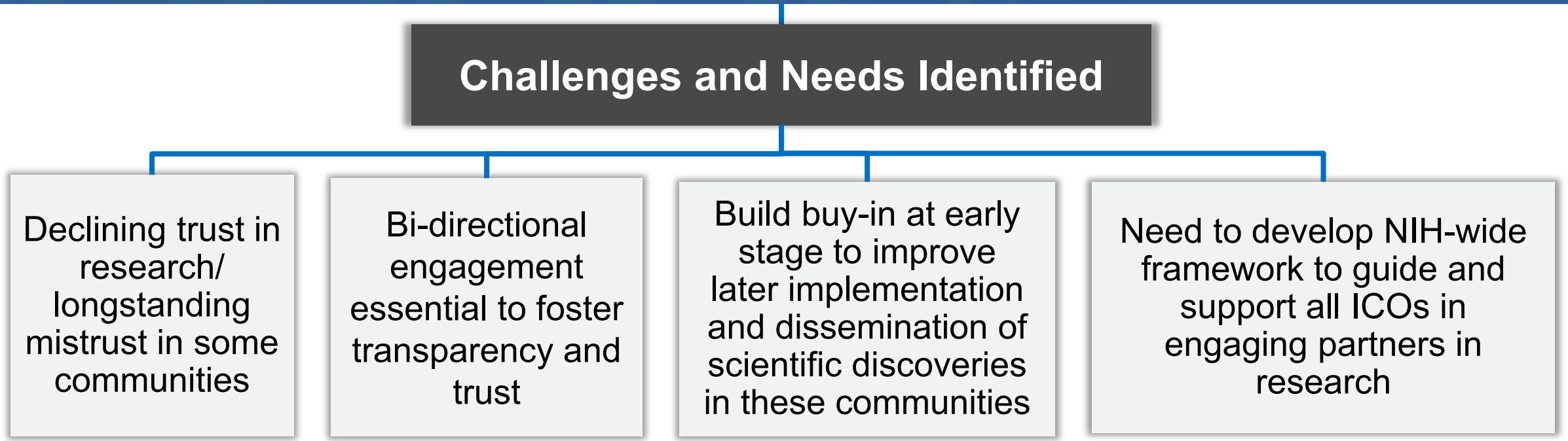
Increase opportunities to enroll diverse populations by facilitating partnerships and engagement with diverse and underrepresented communities

- Establish trust within communities based on long-standing engagement

Increase equity

- Additional data such as socioeconomic status, disaggregated race/ethnicity data beyond that required by OMB

Promote participants as partners in clinical research



- Craft a unified and public vision promoting community engagement as critical to the clinical research enterprise
- Engage participants in development of optimal strategies for planning, implementation and dissemination of research studies

Embrace and implement new research methodologies, strategies and resources

Challenges and Needs Identified

Augment pragmatic clinical trials in real-world settings

- Improve generalizability and strategies for implementation and dissemination for greatest impact on public health
- Facilitate convergence of clinical research and clinical practice
- Workforce and career development

Pursue novel and responsible approaches for utilizing diverse datasets

- NIH working toward a future of interoperability and maximum utility of data from a variety of sources
- Collect, store, use data more effectively
- Maximize utility & integration of Electronic Health Record (EHR) data in clinical research
- Individual-level participant data (IPD) – define and promote best practices
- Address challenges of data use: privacy, proprietary concerns, data standards and interoperability, other

Next Steps for Consideration and Discussion (1)

NIH-wide vision for clinical trials

- Continued consideration of needs, priorities for investments
- Develop new resources and programs to achieve NIH strategic vision
- Leverage strategic partnerships with other agencies and entities
- Effectively partner with the extramural community to advance clinical care and public health

Next Steps for Consideration and Discussion (2)

Develop mechanisms for a 'Learning Clinical Research Ecosystem'

- Maximize ability of all ICOs and programs to learn from each other
- Numerous examples of lessons learned and innovative practices that could benefit all ICOs if widely disseminated
- Help smaller ICOs realize their vision for impactful clinical trials
- Minimize organizational risk by fully leveraging current expertise and resources and maintaining NIH-wide perspective

‘Big Picture’ Questions for Discussion

- What should the role of NIH be, as a major public research funder, in the broader clinical research ecosystem?
- How should NIH best address the urgent need for increased diversity, equity and inclusion in clinical research?
- Clinical research is increasingly interdisciplinary and multi-site – how should we be thinking about new models for working across sectors to increase impactful translation?